CLAIMS

1. A fibrin-containing biological scaffold, which is characterized in that it comprises a mixture consisting of a fibrinogen concentrate obtained from human plasma by a short-time rough purification step and a fibrinogen activator, when a fibrin composition is used in the regeneration of human tissues and the cell growth.

2. The fibrin-containing biological scaffold according to claim 1, wherein said fibrinogen concentrate is obtained by a method comprising steps of cooling the plasma for a short time, rapidly thawing the plasma, and recovering the fibrinogen concentrate.

3. The fibrin-containing biological scaffold according to claim 1 or 2, wherein said fibrinogen concentrate is obtained from the plasma by precipitation, resulting in a recovery rate of fibrinogen within the range between 15% and 32%.

4. The fibrin-containing biological scaffold according to any one of claims 1 to 3, wherein said fibrinogen concentrate is obtained by a method comprising steps of cooling the plasma for 10 to 60 minutes, thawing the plasma for 15 to 60 minutes, and recovering the fibrinogen concentrate.

5. The fibrin-containing biological scaffold according to claim 3 or 4, wherein the cooling step is carried out at a temperature between -20°C and -40°C and the thawing step is carried out at a temperature between −10°C and +15°C.

6. The fibrin-containing biological scaffold according to claim 1, wherein said fibrinogen concentrate is obtained from human plasma using a plasma component fractionation device.

7. The fibrin-containing biological scaffold according to claim 6, wherein said plasma component fractionation device comprises therein a hollow fiber membrane used for fractionation of plasma components.

8. The fibrin-containing biological scaffold according to claim 7, wherein the material for said hollow fiber membrane is any one selected from the group consisting of

hydrophilic polysulfone, EVAL (ethylene-vinyl alcohol copolymer), PAN (polyacrylonitrile), CDA (cellulose diacetate), and CTA (cellulose triacetate).

9. The fibrin-containing biological scaffold according to claim 8, wherein said material for the hollow fiber membrane is hydrophilic polysulfone or EVAL (ethylene-vinyl alcohol copolymer).

10. The fibrin-containing biological scaffold according to any one of claims 6 to 9, wherein the cutoff value of said hollow fiber membrane is between 80,000 daltons and 300,000 daltons.

11. The fibrin-containing biological scaffold according to any one of claims 6 to 9, wherein the cutoff value of said hollow fiber membrane is between 150,000 daltons and 400,000 daltons.

12. The fibrin-containing biological scaffold according to any one of claims 6 to 11, wherein said fibrinogen concentrate is obtained from the end of a hollow fiber by supplying human plasma to a hollow portion of the hollow fiber in a plasma component fractionation device, and allowing mainly liquid components to permeate from the inner surface of the hollow fiber to the outer surface thereof.

13. The fibrin-containing biological scaffold according to claim 12, wherein the ratio (Bin/Bout) between the amount (Bin) of the patient plasma supplied to said hollow portion per unit time and the amount (Bout) of fibrinogen concentrate collected from the end of the hollow fiber per unit time is within the range between 2 and 20.

14. The fibrin-containing biological scaffold according to claim 12 or 13, wherein said Bin/Bout ratio is within the range between 5 and 10.

15. The fibrin-containing biological scaffold according to any one of claims 6 to 14, wherein said fibrinogen concentrate is obtained by allowing human plasma to come into contact with the outer surface of a hollow fiber in a plasma component fractionation device, and allowing mainly liquid components to permeate from the outer surface of the hollow fiber to the inner surface thereof, thereby concentrating the plasma allowed to be

contacted with the outer portion of the hollow fiber.

16. The fibrin-containing biological scaffold according to claim 15, wherein, when liquid components are allowed to permeate, the hollow portion of the hollow fiber is depressurized, and the liquid components are allowed to permeate by aspiration from the outer portion of the hollow fiber to the inner portion thereof.

17. The fibrin-containing biological scaffold according to claim 15 or 16, wherein the ratio (Cinitial/Cend) between the amount (Cinitial) of plasma that is allowed to come into contact with the outer surface of said hollow fiber and the amount (Cend) of a fibrinogen concentrate obtained by allowing mainly liquid components to permeate and by concentrating the plasma that is allowed to be contacted with the outer surface of the hollow fiber is within the range between 2 and 20.

18. The fibrin-containing biological scaffold according to any one of claim 15 to 17, wherein said ratio Cinitial/Cend is within the range between 5 and 10.

19. The fibrin-containing biological scaffold according to any one of claims 15 to 18, wherein the amount of the patient plasma allowed to come into contact with the outer surface of said hollow fiber is between 5×10^{-5} and 5×10^{-4} m^3, the outer surface area of the hollow fiber allowed to come into contact with the plasma is between 0.001 and 1 m^2, and a differential pressure caused by aspiration is between 0.001 and 0.08 MPa.

20. The fibrin-containing biological scaffold according to any one of claims 1 to 19, wherein said fibrinogen activator is thrombin.

21. The fibrin-containing biological scaffold according to claim 20, wherein said thrombin is obtained from the blood of a single person, from which fibrinogen is obtained.

22. The fibrin-containing biological scaffold according to any one of claims 1 to 21, which is used in culture of cells selected from the group consisting of vascular endothelial cells, fibroblasts, keratinocytes, mesenchymal stem cells, osteocytes, osteoblasts, osteoclasts, liver cells, pancreatic cells, and hematopoietic stem cells.

23. The fibrin-containing biological scaffold according to any one of claims 1 to 22, which has a cell growth-stimulating activity that is greater than those in the cases of culturing the cells with no biological scaffold or with a purified fibrinogen concentrate as a control, when at least one type of cells selected from the group consisting of vascular endothelial cells, fibroblasts, keratinocytes, mesenchymal stem cells, osteocytes, osteoblasts, osteoclasts, liver cells, pancreatic cells, and hematopoietic stem cells is cultured.

24. A method for culturing cells or regenerating tissues, which comprises culturing cells using the fibrin-containing biological scaffold according to any one of claims 1 to 23.

25. The method according to claim 24, wherein said cells are selected from the group consisting of vascular endothelial cells, fibroblasts, keratinocytes, mesenchymal stem cells, osteocytes, osteoblasts, osteoclasts, liver cells, pancreatic cells, and hematopoietic stem cells.

26. The method according to claim 24 or 25, wherein the above cells are derived from a single person, from who plasma used as a starting material for a fibrinogen concentrate is collected.

27. The method according to any one of claims 24 to 26, wherein the culture is carried out in the presence of a substance that stimulates cell growth and/or differentiation.

28. The method according to claim 27, wherein said substance that stimulates cell growth and/or differentiation is a substance which is released from platelets.

29. The method according to claim 28, wherein said substance released from platelets is obtained by a method comprising the following steps:

(1) a step of allowing the whole blood to flow through a first-stage filter for giving passage to erythrocytes, platelets and plasma, and adsorbing leukocytes, so as to obtain fractions permeated through the filter;

(2) a step of allowing the permeated fractions obtained in (1) above to flow through a second-stage filter for adsorbing platelets and giving passage to erythrocytes, so as to obtain a filter on which platelets are adsorbed; and

(3) a step of allowing a recovery solution containing a platelet activator to flow through the filter obtained in (2) above, so as to obtain a solution containing an activated platelet-released substance.

30. The method according to claim 29, wherein said platelet activator is at least one substance selected from the group consisting of ATP, ADP, collagen, and thrombin.

31. The method according to claim 27, wherein said substance that stimulates cell growth and/or differentiation is a substance which is released from leukocytes.

32. The method according to claim 31, wherein said substance released from leukocytes is obtained by a method comprising the following steps:

(1) a step of allowing the whole blood to flow through a first-stage filter for giving passage to erythrocytes, platelets and plasma, and adsorbing leukocytes, so as to obtain a filter on which leukocytes are adsorbed; and

(2) a step of allowing a recovery solution containing a leukocyte activator to flow through the filter obtained in (1) above, so as to obtain a solution containing an activated leukocyte-released substance.

33. The method according to claim 27, wherein said substance that stimulates cell growth and/or differentiation is a mixture consisting of a substance released from platelets and a substance released from leukocytes.

34. The method according to claim 33, wherein said mixture consisting of a substance released from platelets and a substance released from leukocytes is obtained by a method comprising the following steps:

(1) a step of allowing the whole blood to flow through a filter for giving passage to erythrocytes and plasma and adsorbing platelets and leukocytes, so as to obtain a filter on which platelets and leukocytes are adsorbed; and

(2) a step of allowing a recovery solution containing a platelet activator and a leukocyte activator to flow through the filter obtained in (1) above, so as to obtain a solution containing an activated platelet-released substance and an activated leukocyte-released substance.

35. The method according to any one of claims 24 to 34, wherein the cells are obtained by allowing cells derived from a human to flow through a filter.

36. The method according to any one of claims 24 to 34, wherein the plasma used as a starting material for a fibrinogen concentrate is obtained by allowing human blood to flow through a filter.

37. A cell culture or regenerated tissue supported on a scaffold, which is obtained by the method according to any one of claims 24 to 36.

38. A method for promoting tissue regeneration, wherein the cell culture or regenerated tissue according to claim 37 is applied to damaged tissues, or is used as a graft.

39. A method for promoting tissue regeneration, which comprises a step of adding to damaged tissues a mixture obtained by mixing the biological scaffold according to any one of claims 1 to 23 and cells.

40. The method for promoting tissue regeneration according to claim 39, wherein said cells are at least one type of cells selected from the group consisting of vascular endothelial cells, fibroblasts, keratinocytes, mesenchymal stem cells, osteocytes, osteoblasts, osteoclasts, liver cells, pancreatic cells, and hematopoietic stem cells.

41. A concentration system for obtaining a fibrin-containing biological scaffold, which comprises the following means:

(1) a means for roughly purifying human plasma by a plasma component fractionation membrane;

(2) a means for introducing human plasma into the surface of said membrane; and

(3) a means for obtaining a fibrinogen concentrate from the surface of said membrane.

42. The system according to claim 41, which is characterized in that the cutoff value of said plasma component fractionation membrane is between 80,000 daltons and 300,000 daltons.

43. The system according to claim 41, which is characterized in that the cutoff value of said plasma component fractionation membrane is between 150,000 daltons and 400,000 daltons.

44. The concentration system according to claim 42 or 43, wherein said plasma component fractionation membrane is a hollow fiber membrane.

45. The system according to claim 44, which is characterized in that the material for said hollow fiber membrane is any one selected from the group consisting of hydrophilic polysulfone, EVAL (ethylene-vinyl alcohol copolymer), PAN (polyacrylonitrile), CDA (cellulose diacetate), and CTA (cellulose triacetate).

46. The system according to claim 45, wherein said material for the hollow fiber membrane is hydrophilic polysulfone or EVAL (ethylene-vinyl alcohol copolymer).

47. The concentration system according to any one of claims 41 to 46, wherein said introducing means is a liquid-supplying or liquid-aspirating device for introducing human plasma from one of flow ports provided on said fractionation device into the inner or outer membrane surface of the hollow fiber membrane and discharging it from another flow port.

48. The concentration system according to any one of claims 41 to 47, wherein said means for obtaining said concentrate is a means for storing the concentrate that is connected to one of the flow ports provided on said fractionation device.

49. The concentration system according to any one of claims 41 to 48, wherein said rough purification means is a plasma component fractionation device where both ends of a hollow fiber membrane built in a vessel are potted such that the inner portion of the hollow is communicated with the outer portion of the vessel.

50. The concentration system according to any one of claims 41 to 48, wherein said

rough purification means is a plasma component fractionation device where one end of a hollow fiber membrane built in a vessel is potted such that the inner portion of the hollow is communicated with the outer portion of the vessel, and the other end is sealed.

51. A method for operating the concentration system according to claim 49, which comprises supplying human plasma to a hollow portion of the follow fiber in a plasma component fractionation device, allowing mainly liquid components to permeate from the inner surface of the hollow fiber to the outer surface thereof, and collecting a fibrinogen concentrate from the end of the hollow fiber.

52. The method for operating the concentration system according to claim 51, wherein the ratio (Bin/Bout) between the amount of the patient plasma supplied to said hollow portion per unit time (Bin) and the amount of fibrinogen concentrate collected from the end of the hollow fiber per unit time (Bout) is within the range between 2 and 20.

53. The method for operating the concentration system according to claim 52, wherein said Bin/Bout ratio is within the range between 5 and 10.

54. A method for operating the concentration system according to claim 50, which comprises allowing human plasma to come into contact with the outer surface of a hollow fiber in a plasma component fractionation device, allowing mainly liquid components to permeate from the outer surface of the hollow fiber to the inner surface thereof, and concentrating the plasma allowed to be contacted with the outer portion of the hollow fiber, so as to obtain a fibrinogen concentrate.

55. The method for operating the concentration system according to claim 54, which comprises allowing plasma to come into contact with the outer surface of a hollow fiber, and depressurizing the hollow portion of the hollow fiber when mainly liquid components are allowed to permeate from the outer surface of the hollow fiber to the inner surface thereof, so that said components are allowed to permeate by aspiration from the outer portion of the hollow fiber to the inner portion thereof.

56. The method for operating the concentration system according to claim 55, wherein said ratio Cinitial/Cend between the amount (Cinitial) of plasma that is allowed to come into contact with the outer surface of said hollow fiber and the amount (Cend) of a fibrinogen concentrate obtained by allowing mainly liquid components to permeate and concentrating the plasma that is allowed to be contacted with the outer surface of the hollow fiber is within the range between 2 and 20.

57. The method for operating the concentration system according to claim 54, wherein said ratio Cinitial/Cend is within the range between 5 and 10.

58. The method for operating the concentration system according to any one of claims 54 to 57, wherein the amount of the patient plasma allowed to come into contact with the outer surface of said hollow fiber is between 5×10^{-5} and 5×10^{-4} m^3, the outer surface area of the hollow fiber allowed to come into contact with the plasma is between 0.001 and 1 m^2, and a differential pressure caused by aspiration is between 0.001 and 0.08 MPa.

59. A system for producing a fibrin-containing biological scaffold, which comprises the following means:

(1) a means for fractionating human plasma by a plasma component fractionation membrane having a cutoff value between 80,000 daltons and 300,000 daltons, so as to separate a fibrinogen concentrate from the residual fractionated plasma;

(2) a means for recovering said fibrinogen concentrate and the residual fractionated plasma, separately;

(3) a means for producing fibrin glue from said fibrinogen concentrate; and

(4) a means for recycling the residual fractionated plasma.

60. A system for producing a fibrin-containing biological scaffold, which comprises the following means:

(1) a means for fractionating human plasma by a plasma component fractionation membrane having a cutoff value between 150,000 daltons and 400,000 daltons, so as to

separate a fibrinogen concentrate from the residual fractionated plasma;

(2) a means for recovering said fibrinogen concentrate and the residual fractionated plasma, separately;

(3) a means for producing fibrin glue from said fibrinogen concentrate; and

(4) a means for recycling the residual fractionated plasma.

61. The system according to claim 59 or 60, wherein said human plasma is plasma which is collected by continuous extracorporeal circulation.

62. The system according to any one of claims 59 to 61, wherein said means for collecting human plasma has a means for separating plasma from the whole blood.

63. The system according to any one of claims 59 to 62, wherein said means for separating human plasma is gravity separation, centrifugation, or a membrane separation means.

64. The system according to any one of claims 59 to 63, wherein activated thrombin plasma is prepared from human plasma that is used to obtain a fibrinogen concentrate.

65. The system according to any one of claims 59 to 64, wherein an activated thrombin solution is obtained from said fibrinogen concentrate.

66. The system according to any one of claims 59 to 65, wherein the residual fractionated plasma obtained as a result of the fractionation by a plasma component fractionation membrane is used to prepare activated thrombin plasma.

67. The system according to any one of claims 59 to 66, wherein the residual fractionated plasma obtained as a result of the fractionation by a plasma component fractionation membrane is mixed with plasma-separated blood, from which plasma has been separated by a plasma separation means, and the mixture is then returned to a human body.

68. The system according to any one of claims 59 to 67, wherein said recovery system has a means for storing the obtained fibrinogen concentrate in the form of plasma containing a fibrinogen concentrate derived from a single donor.

69. The system according to any one of claims 59 to 68, wherein said means for producing fibrin glue has a means for mixing a fibrinogen concentrate, a fibrin stabilizing factor, and a fibrinogen activating factor.

70. A method for producing a fibrin-containing biological scaffold, which comprises the following steps:

(1) a step of fractionating human plasma by a plasma component fractionation membrane having a cutoff value between 80,000 daltons and 300,000 daltons, so as to separate a fibrinogen concentrate from the residual fractionated plasma;

(2) a step of recovering separately a high molecular weight fractionated plasma containing a large amount of fibrinogen concentrate and the residual fractionated plasma;

(3) a step of producing fibrin glue from said high molecular weight fractionated plasma containing a large amount of fibrinogen concentrate; and

(4) a step of recycling the residual fractionated plasma.

71. A method for producing a fibrin-containing biological scaffold, which comprises the following steps:

(1) a step of fractionating human plasma by a plasma component fractionation membrane having a cutoff value between 150,000 daltons and 400,000 daltons, so as to separate a fibrinogen concentrate from the residual fractionated plasma;

(2) a step of recovering separately a high molecular weight fractionated plasma containing a large amount of fibrinogen concentrate and the residual fractionated plasma;

(3) a step of producing fibrin glue from said high molecular weight fractionated plasma containing a large amount of fibrinogen concentrate; and

(4) a step of recycling the residual fractionated plasma.

72. The method according to claim 70 or 71, which comprises a step of collecting said human plasma by continuous extracorporeal circulation.

73. The method according to any one of claims 70 to 72, wherein said step of collecting human plasma comprises a step of separating plasma from the whole blood.

74. The method according to any one of claims 70 to 73, wherein said step of separating plasma is gravity separation, centrifugation, or a membrane separation step.

75. The method according to any one of claims 70 to 74, wherein the residual fractionated plasma obtained as a result of the fractionation by a plasma component fractionation membrane is mixed with plasma-separated blood, from which plasma has been separated by the plasma separation means, and the mixture is then returned to a human body.

76. The method according to any one of claims 70 to 75, wherein said recovery step comprises a step of storing the obtained fibrinogen concentrate in the form of fibrinogen concentrated plasma derived from a single donor.

77. The method according to any one of claims 70 to 76, wherein the step of producing fibrin glue comprises a step of mixing a high molecular weight fractionated plasma containing a large amount of fibrinogen, a fibrin stabilizing factor, and a fibrinogen activating factor.